

## A New Fitness Function and its Application on a five Locus Model

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**Summary.** A new fitness function is proposed. It is a balance function which results from a combination of a turnover function defining the expression of favourable genetic factors and a cost function describing the costs of metabolism. A favourable genetic factor is defined as the heterozygote state at a locus. Five loci with two alleles each are considered. In computer simulations various kinds of this function are investigated. Their influence on the genetic composition of a population in equilibrium, the number and types of equilibria and the mean fitness are reported. Free recombination and tight linkage are considered.

### Introduction

The fitness of an individual is a quantitative trait. Quantitative traits are usually only parts of the whole phenotype (e.g. content of certain substances, size, yield etc.). There are only special gene loci involved in the expression of such traits. In addition, merely those parts of their effects can be recognized which are related directly to the trait measured. In contrast, fitness includes the action of all genes of an individual and is further determined by all effects of the different genes. Consequently the fitness value reflects not only the advantage of all favourable factors present but also the metabolic costs emerging from the operation of these factors.

Favourable factors may be the functional alleles of a locus in a simple case or special combinations of alleles if all alleles taken into consideration are functional. Whereas both alleles of a homozygote code for only one type of an enzyme, in heterozygote genotypes, 2 different enzymes are possible allowing improved adaptation to different environments. In such situations the heterozygote state of a gene locus may be a favourable factor.

It is assumed that the genes involved in the expression of quantitative characters have similar and cumulative actions. While cumulative action of genes has often been proved (Mather and Jinks 1971; Sirks 1956), very little is known about the way cumulative genes interact. It is often assumed that the action of

a single gene is independent of the number of genes effective in an individual. There are arguments, however, for considering interactions (e.g. physiological limits on the gene action, regulatory effects). The advantage of a favourable substitution at one locus is less than expected if other loci are already favourably substituted. Thus, the degree of expression of a character may follow a saturation curve, which is governed by the number of genes acting.

Investigations on the gene dosage effect in polyploids have shown, in the case of one locus, that with increasing numbers of functional alleles a saturation could be observed (Seyffert 1956, 1957, 1959). The results of investigations on the dosage effect of the Bar duplication support this assumption (Anders et al. 1967; Chevais 1943). Furthermore, in studies on dependence of cell size and plant height on the number of genomes in polyploids, saturation effects were shown.

An example of a multilocus case has been reported recently by Forkmann and Seyffert (in press). In these investigations all possible homozygote and heterozygote combinations of three loci influencing the concentration of anthocyanins in flowers have been measured and plotted against the number of functional alleles. The anthocyanin concentration follows a saturation curve. Considering all these facts it seems reasonable to conclude that saturation effects are widespread in nature and may play an important role in the expression of fitness.

As mentioned earlier, metabolic costs have to be taken into account. Measurements concerning such costs are not yet available. Since, in this case too, a quantitative trait is being considered, some saturation effects are to be expected. Under certain conditions the costs of a favourable substitution at a locus may exceed the attainable advantage. A substitution in the region of saturation gives, for instance, no further advantage but increases the costs of metabolism. Thus, the fitness of an individual with a very high number of favourable genetic factors may be less than the fitness of an individual with an optimal number of favourable genes. Therefore the fitness of genotypes can not be defined by a single saturation curve: in addition a second function should be used. The functions are

1. A turnover function which defines the expression of the genetic factors (TF).
2. A cost function which describes the costs of the metabolism or turnover, resp. (CF).

In this paper, a model will be presented considering the fitness systems as described above. In particular their influence on the structure of populations in equilibrium (gametic frequencies) will be considered.

#### The simulation method

Five loci, with two alleles each, are considered. The populations are assumed to be panmictic and infinite in size. The genetic composition of the populations can be described by the frequencies of the 32 possible gametes. Random mating results in 528 distinguishable types of zygotes if all repulsion and coupling phases are considered in the multiple heterozygote genotypes. On the basis of the 528 zygote frequencies the values for all possible linkage disequilibria can be calculated.

Each population was started with 32 gametes, the frequencies of which were chosen by using a computer program for random variables. Random combinations of gametes lead to the zygote frequencies. The selection acts on the zygotes corresponding to a fitness function which is defined in detail below. Recombination is taken into account in the formation of the gametes in the following generations. An equilibrium is assumed when the frequencies of each of the 32 gametes of one

generation do not differ by a value of more than  $10^{-6}$  from those in the previous generation.

#### The fitness function

The fitness function is composed of a turnover function and a cost function. Both functions have a sigmoid shape. In the absence of favourable genetic factors (complete homozygote genotypes) the turnover function starts with a minimum value unequal to zero. The reasons for this are given by an excellent formulation by Wills and Miller (1976): "Because all the alleles are functional, the ability of an organism to survive and leave offspring under uncrowded and un-stressful conditions would not be impaired even it were completely homozygous for the alleles of all selected functional polymorphisms in a population". In contrast the cost function starts with zero. Each favourable factor added to the system causes an increase in the turnover and the cost, respectively. When a certain number of favourable factors is reached a saturation effect occurs.

Functions of this kind are well known in enzyme kinetics (Mahler and Cordes 1971). Therefore they can be defined by formulae elaborated for this type of function. In enzyme kinetics the parameters are related to specific characteristics of enzymatic reactions. In our case they are used to formulate mathematically the curves desired.

$$\text{The turnover function: } TF = C_1 + \frac{N(1+N)C_3^{-1}}{C_4 + (1+N)C_3}$$

$$\text{The cost function: } CF = \frac{C_2 N(1+N)C_3^{-1}}{C_5 + (1+N)C_3}.$$

Where,  $C_1$  = Minimum value of the turnover function

$C_2$  = Maximum value of the cost function

$C_3, C_4, C_5$  = Parameter determining the range of the slope of the turnover function and the cost function, resp. .

$N$  = Number of favourable genetic factors.

The description of the fitness of different desired genotypes is obtained by the combination of both functions into a single balance function.

Table 1. Fitness values calculated for the fitness systems 1-10 by means of the balance functions and fitness values of the threshold models (systems 11-13). The fitness values calculated from the balance function were normalized to the maximum value of each function. The position of the steepest slope of the fitness function determined by the degree of the heterozygosity is listed in the last column

fitness system	0	1	2	3	4	5	steepest slope
1	.319	.349	.444	.606	.804	1.000	3-4-5
2	.374	.377	.422	.613	.898	1.000	3-4
3	.580	.582	.615	.792	1.000	.977	(2)-3-4
4	.239	.283	.463	.727	.911	1.000	2-3-(4)
5	.442	.480	.693	.932	1.000	.985	2-3
6	.397	.417	.632	1.000	.985	.802	2-3
7	.510	.587	.809	.936	.982	1.000	1-2-(3)
8	.244	.389	.800	.998	1.000	.936	1-2-(3)
9	.248	.396	.810	1.000	.991	.927	1-2-(3)
10	.277	.541	1.000	.992	.914	.888	1-2
11	.500	.500	.500	.500	1.000	1.000	3-4
12	.500	.500	.500	1.000	1.000	1.000	2-3
13	.500	.500	1.000	1.000	1.000	1.000	1-2

Table 2. Parameter of the fitness function

fitness system	c <sub>1</sub>	c <sub>2</sub>	c <sub>3</sub>	c <sub>4</sub>	c <sub>5</sub>
1	.2	.1	3	200	3 000
2	.2	.8	6	14 000	55 000
3	.2	.9	7	55 000	95 000
4	.2	.5	4	200	5 000
5	.4	.5	5	400	3 000
6	.2	.9	6	2 500	13 000
7	.8	.1	5	100	4 000
8	.2	.1	5	100	5 000
9	.2	.5	5	100	4 000
10	.2	.5	6	100	3 000

$$\text{The balance function: } BF = C_1 + \frac{N(1+N)^{C_3-1}}{C_4 + (1+N)^{C_3}} - \frac{C_2 N(1+N)^{C_3-1}}{C_5 + (1+N)^{C_3}}$$

The maximum of the balance function describes the situation where the most profit from turnover and cost is achieved. This corresponds to the optimum number of favourable genetic factors.

In the present investigation a favourable factor is defined as the heterozygote state at a locus. Both homozygote genotypes of a locus have the same disadvantage. The fitness of a complete genotype is de-

fined by the number of heterotic loci according to the balance function. The increments of the corresponding genotypes have the same value for all loci. The model is therefore a special case of the symmetric viability model.

The fitness systems will be classified either by the position of the steepest slope or by the position of the maximum of the curve, both described in terms of the number of heterozygous loci (Table 1). The parameters of the functions have been chosen in such a way that the influence of the fitness systems differing in this respect on the genotypic composition of the populations under equilibrium conditions could be investigated (Table 2). Each of the Figs. (1-10) shows the turnover function, the cost function and the balance function of the fitness system listed in Table 2. The results will be discussed in comparison with those of three threshold models.

## Results

The fitness system used represents a special case of the general symmetric viability model. Thus a comparison of our results with those of Karlin and Feldman (1970) and Feldman et al. (1974), who found mostly symmetric equilibria, is possible. Complementary gametes are in equal frequencies in a sym-

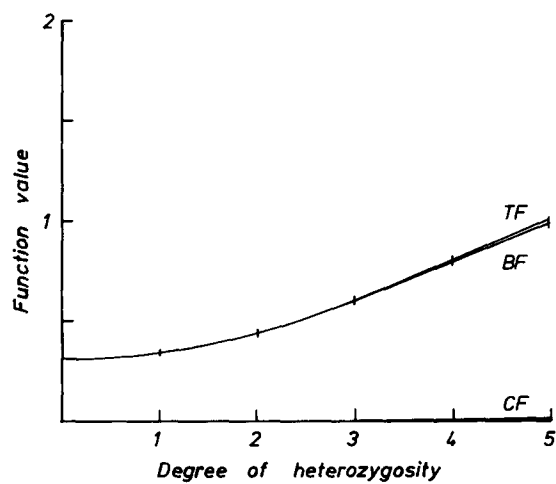


Fig. 1

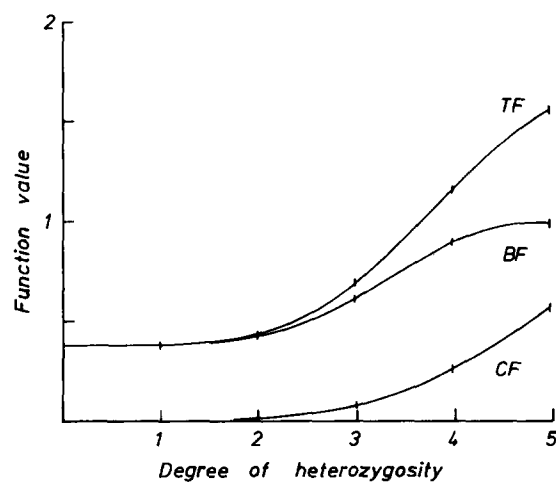


Fig. 2

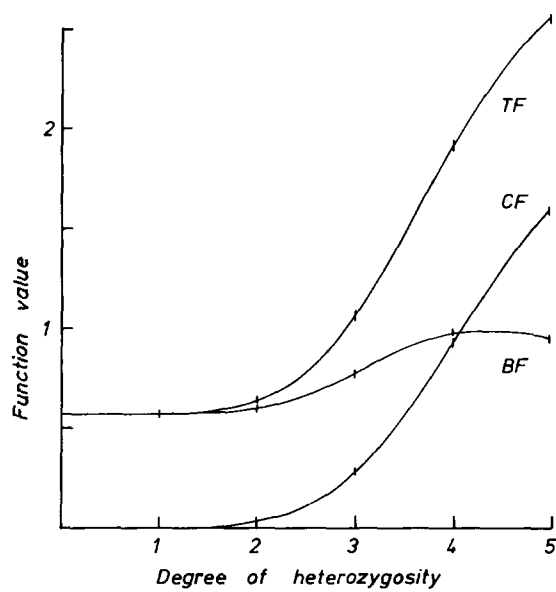


Fig. 3

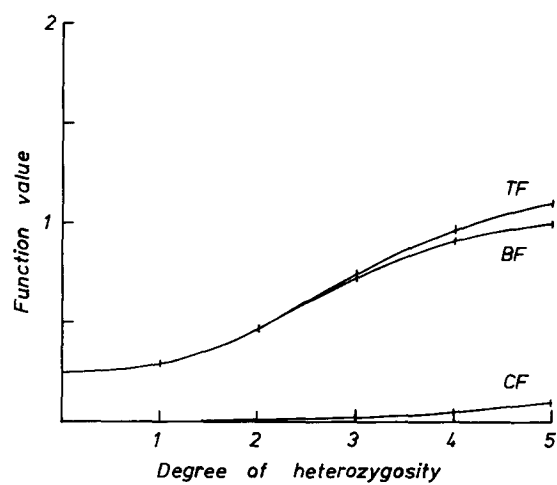


Fig. 4

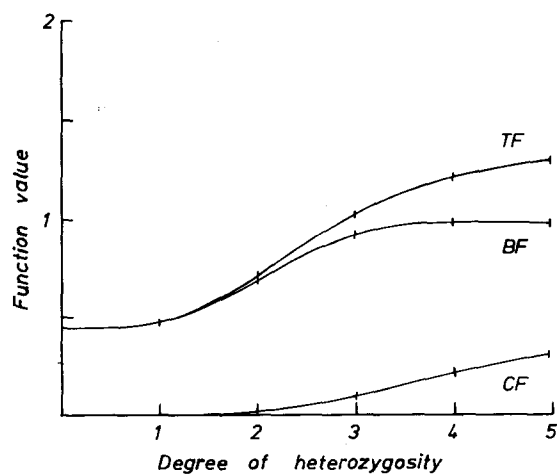


Fig. 5

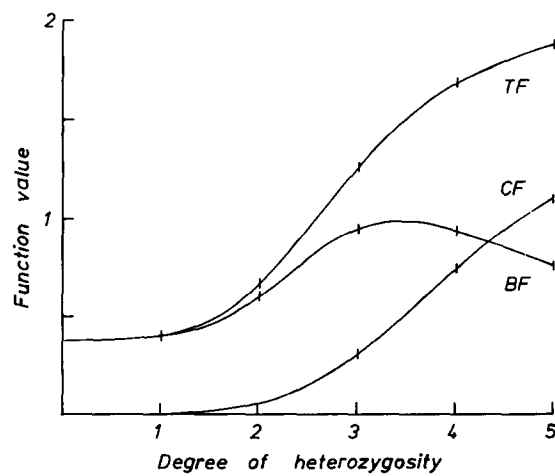


Fig. 6

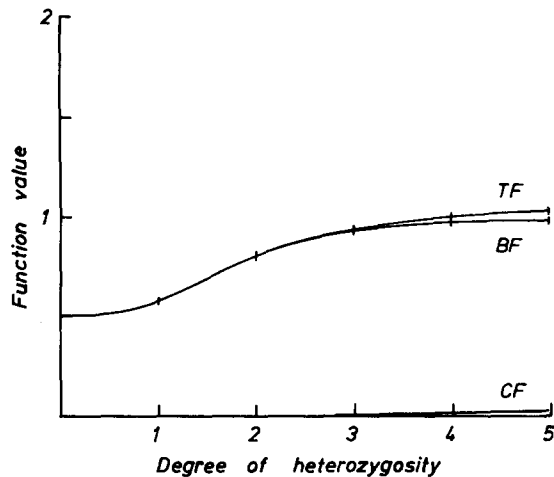


Fig. 7

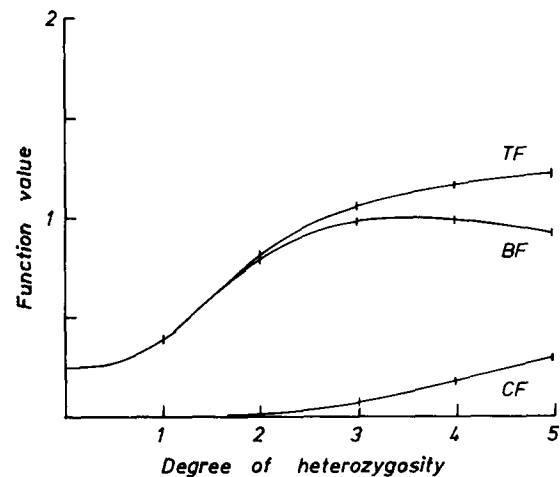


Fig. 8

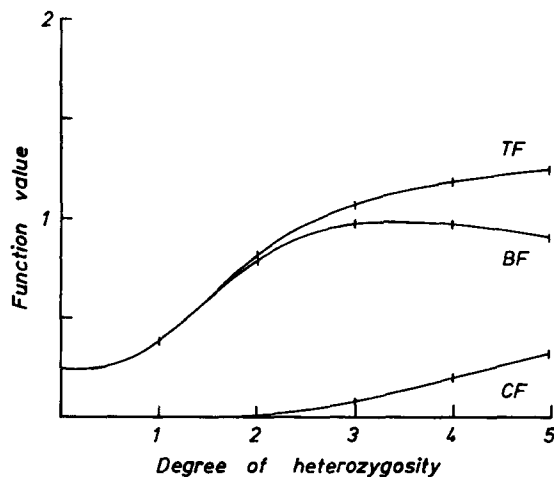


Fig. 9

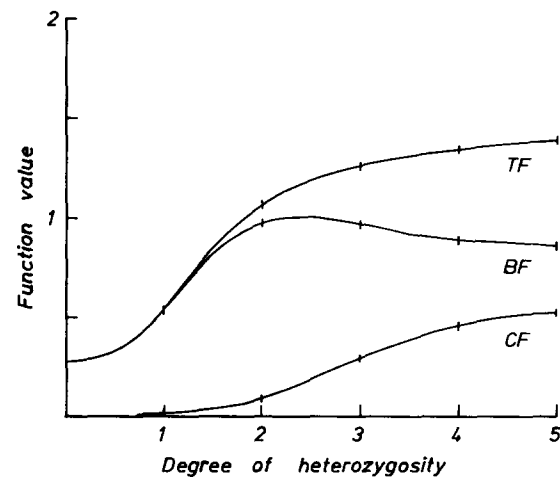


Fig. 10

Figs. 1-10. The relationship between the values of the turnover function (TF), the cost function (CF), balance function (BF) and the degree of heterozygosity (Parameters of the functions are described in Table 2)

metric equilibrium (Karlin and Feldman 1970). Thus  $g(AB) = g(ab)$  and  $g(Ab) = g(aB)$  in a two locus case. A special case of the symmetric equilibrium is the central solution, in which all possible gametes exist in equal frequencies. In the two locus case Karlin and Feldman (1970) proved the existence of both symmetric and asymmetric equilibria. In the latter case all gene frequencies differ from 0.5. Moreover Feldman et al. (1974) showed asymmetric equilibria with  $p_i = 0.5$  for the three locus case.

Our investigations result in the central solution of all fitness systems considering a recombination rate of 0.5 (Table 3). In the case of tight linkage

( $r = 0.001$ ), however, both symmetric and asymmetric equilibria are possible. In the latter case  $p_i \neq 0.5$  and  $p_i = 0.5$  both occur. The results of systems with tight linkage will be discussed in detail below. Gametes with frequencies  $g_i > 1/32$  are termed frequent gametes (FG).

#### 1. Symmetric equilibria, $p_i = 0.5$

Symmetric equilibria with  $p_i = 0.5$  are found for the fitness systems 1 and 2 only (Table 3). They are characterized by two complementary gametes (FG)

Table 3. Computer results of the fitness systems 1-13.  $\bar{W}$  = mean fitness (free recombination),  $\bar{W}_{\max}$ ,  $\bar{W}_{\min}$  = mean fitness values ( $r = 0.001$ ),  $n$  = number of frequent gametes (FG),  $\Sigma_{\max}$ ,  $\Sigma_{\min}$  = maximum and minimum sum of the frequent gametes,  $L_{\max}$ ,  $L_{\min}$  = maximum and minimum percentage of reduced load  
\* $r = 0.01$

fitness system	$r = 0.5$ $\bar{W}$	$p_i = 0.5$				$r = 0.001$ $p_i \neq 0.5$			
		$n$ $> 1/32$	$\Sigma_{\max}$	$\bar{W}_{\max}$	$L_{\max}$	$n$	$\Sigma_{\max}$	$\bar{W}_{\max}$	$L_{\max}$
			$\Sigma_{\min}$	$\bar{W}_{\min}$	$L_{\min}$		$\Sigma_{\min}$	$\bar{W}_{\min}$	$L_{\min}$
1	.5495	2	.9802	.6555	23.52	-	-	-	-
2	.5656	2	.9738	.6830	27.03	-	-	-	-
3a	.7355	4	.9690	.7874	19.62	6	.9664	.7931	20.76
b		4	.9696	.7946	22.34				
			.9714	.7949	22.46				
4	.5953	4	.9620	.6440	12.03	5/6	.9471	.6314	8.92
			.9756	.6447	12.21		.9583	.6317	8.99
5	.7837	4	.9212	.8216	17.52	-	-	-	-
			.9620	.8221	17.75				
6	.7665	4	.9588	.8405	31.69	-	-	-	-
			.9836	.8415	32.12				
7	.8377	8	.8944	.8520	8.81	8	.8424	.8485	6.65
			.9280	.8530	9.43				
8	.8158	8	.9480	.8496	18.35	8	.9210	.8418	14.12
			.9684	.8506	18.89				
9	.8191	8	.9464	.8525	18.46	8	.8920	.8443	13.93
			.9648	.8534	18.96		.8968	.8444	13.98
10	.8862	16	.9760	.9241	33.30	-	-	-	-
11*	.5938	2 + 4	.9280	.7202	31.11	-	-	-	-
12*	.7500	4	.7596	.8221	28.84	-	-	-	-
			.8548	.8332	33.28				
13*	.9063	16	.8048	.9293	24.55	-	-	-	-

having very high frequencies, which account for 98% of all gametes in the population. Under the condition of a five locus model there are 16 different possibilities for such complementary FGs. All equilibria are equivalent and the populations have the same mean fitness. All gene pairs are in pairwise linkage disequilibrium ( $D_{ij}$ ). These results correspond to those from the multiplicative model (Lewontin 1964).

## 2. Asymmetric equilibria, $p_i = 0.5$

Asymmetric equilibria with a gene frequency of  $p_i = 0.5$  are found in the fitness systems 3 to 10 (Table 3). They can be classified by the number of FGs (2, 4, 8 and 16). In all these cases the FGs occur in equal proportions.

### 2.1. Equilibria with 4 frequent gametes (FG)

These equilibria occur in the fitness systems 3, 4, 5 and 6. The four gametes comprise 92-98% of all gametes, depending on the fitness system.

In the simulations carried out, two pairwise linkage disequilibria ( $D_{ij}$ ) for each system have been found. It could be shown that without exception four of the five loci are involved in the formation of the pairwise  $D_{ij}$ . There are 15 different combinations between two pairwise  $D_{ij}$  satisfying these conditions. Furthermore, both the repulsion and coupling phases have to be considered for each  $D_{ij}$ ; these are designated as (-) and (+) respectively. As the two loci involved are independent with regard to phase, there are four possibilities for each  $D_{ij}$  (++ , +- , -+ , --). Thus  $15 \times 4 = 60$  combinations are possible. For each of these combinations two ways exist to link them with

the fifth locus. Consequently a total of 120 equilibria should be expected.

These combinatorial statements have been confirmed in 54 computer runs. In these runs 14 out of 15 possible combinations between two pairwise  $D_{ij}$  have been verified. Furthermore, all four combinations in respect to repulsion and coupling phase have been found. In one case of pairwise linkage disequilibria ( $D_{AB} = 0.246$  and  $D_{DE} = -0.246$ , 6<sup>th</sup> fitness system) both possibilities have been observed to connect the fifth locus. The alternative combinations are

AB C De, AB c dE, ab C dE, ab c De and  
AB C dE, AB c De, ab C DE, ab c dE.

In 54 runs 6 of the theoretical equilibria have been verified twice.

The frequencies of the four FGs are influenced by the recombination rate ( $r_{ij}$ ) between the loci involved in the formation of the corresponding pairwise  $D_{ij}$ . Small recombination rates allow higher values of the  $D_{ij}$  leading to higher mean fitness values. In Table 3 the maximum and the minimum values of the FGs and the mean fitness are listed. Both have been calculated in the computer runs for the various fitness systems. These facts are demonstrable by an example of the fourth fitness system:

Loci	$r_{ij}$	FG	$\bar{W}$	$D_{ij}$
AB, DE	0.001	0.2439	0.6447	0.2460
AD, BE	0.003	0.2405	0.6440	0.2384

The fitness system 3 is a special case. The type of equilibrium described above has been verified only once in 7 runs (3a in Table 3). In two further runs additional asymmetric equilibria with  $p_i = 0.5$  and with four FGs but with three pairwise  $D_{ij}$  have also been found (3b in Table 3). In these  $D_{ij}$ , only three loci are involved, only two of which are independent. Four combinations (++ , +- , -+ , --) between both independent  $D_{ij}$  are possible. Furthermore, 10 different combinations resulted from the five loci investigated. Thus  $10 \times 4 = 40$  different equilibria of this type will be obtained. Analogous to the results which have been described above, the recombination rates between the three loci involved in the  $D_{ij}$  determine the value of the mean fitness. Thus, a higher value than in case 3a is always found (Table 3). In total,

$120 + 40 = 160$  different asymmetric equilibria with  $p_i = 0.5$  are to be expected for the third fitness system.

## 2.2. Equilibria with 8 frequent gametes (FG)

Equilibria of this type have been found in the fitness systems 7, 8 and 9. No pairwise linkage disequilibria have occurred. Formulae for the calculation of disequilibria of third order were given by Bennett (1954).

$$D_{123} = G_1 - p_1 D_{23} - p_2 D_{13} - p_3 D_{12} - p_1 p_2 p_3. \text{ As in this case}$$

$$D_{12} = D_{13} = D_{23} = 0$$

$$D_{123} = G_1 - p_1 p_2 p_3 \text{ follows.}$$

Two linkage disequilibria of the third order ( $D_{ijk}$ ) could be shown to exist in each of the fitness systems 7, 8 and 9. Analogous to the results described above 10 different  $D_{ijk}$  are possible if 5 loci are considered, one of which is involved twice (e.g.  $D_{ABC}$  and  $D_{CDE}$  unequal 0). In this system there are also 15 possibilities for combinations of the  $D_{ijk}$  pairs. Considering the repulsion phase, and the fact that in this case no independent locus exists, only 60 equilibria are possible.

Under these conditions different recombination rates can be assumed between the loci in question. Again, small recombination rates lead to higher values of the  $D_{ijk}$  and therefore to higher mean fitness values.

A maximum of  $D_{ijk}$  will be reached if the recombination probabilities between the loci in question are small. Thus the loci must be adjacent in our model. This condition is satisfied only by the combinations  $D_{ABC}$  and  $D_{CDE}$ , having only one locus involved twice in the  $D_{ijk}$ .

Such a case has been found in the fitness system 7 (Table 3). In equilibrium the following FGs are present:

ABCDE, ABCde, AbcDe, AbcdE, aBcDe, aBcdE, abCDE and abCde. The frequencies are  $g_i = 0.1160$  and the mean fitness has the value 0.8530. As expected these are the highest values for the  $g_i$  and  $\bar{W}$  obtained in the runs (Table 3). Again, under the conditions of this system, four of the possible equilibria have been verified twice in 32 runs.

### 2.3. Equilibria with 16 frequent gametes (FG)

In fitness system 10, no pairwise linkage disequilibria exist. However, higher order disequilibria have to be assumed. In this case 16 gametes have equal frequencies allowing two different equilibria only. In 10 computer runs these equilibria have been verified five times each. The most frequent gametes are those that have either one, three, five or zero, two, four alleles marked by capital letters (e.g.: Abcde, AbcDE, ABCDE or abcde, abcDE, ABCDe etc.)

### 3. Asymmetric equilibria, $p \neq 0.5$

In 38 runs 5 asymmetric equilibria of this kind have been found in the systems 7, 8 and 9 in addition to the equilibria described above. In these cases three gene frequencies deviate from 0.5. In the computer runs only four of the 10 possible pairwise  $D_{ij}$  have been obtained. These are the  $D_{ij}$  between the two loci having a frequency of 0.5 and those between loci having alleles in unequal frequencies. For example:  $p_A \neq 0.5$ ,  $p_B \neq 0.5$ ,  $p_C \neq 0.5$  and  $p_D = p_E = 0.5$ ,  $D_{AB}$ ,  $D_{AC}$ ,  $D_{BC}$  and  $D_{DE} \neq 0$ .

There are 10 possibilities of combining the three loci where the gene frequencies deviate from 0.5. Moreover, these deviations may be positive or negative. As all loci are independent in this respect there are a total of  $2^3 = 8$  possible combinations. Thus  $8 \times 10 = 80$  equilibria have to be expected. In equilibrium these systems have 8 frequent gametes (FG), which can be classified into four groups with two gametes each of equal frequencies. The value of the four  $D_{ij}$  depends on the recombination rates. These rates differ according to the loci involved. Thus different values of the sum of the eight FGs and the mean fitness also have to be expected, and this was indeed shown to be the case in the fitness system 9. It is reasonable to assume that such a relation also holds for systems 7 and 8.

In seven runs, four asymmetric equilibria have been found in system 3. In each case the gene frequencies deviate from 0.5 at each locus. In contrast to systems 7, 8 and 9 all pairwise  $D_{ij}$  exist, each showing in every equilibrium the same absolute value. There is one most frequent gamete ( $g_i \approx 0.47$ ) and 5

less frequent gametes ( $g_i \approx 0.10$ ). Finally, as there are 32 types of gametes, 32 different equilibria have to be expected.

In system 4, four of 20 populations are in asymmetric equilibrium, in which the frequencies of all loci deviate from 0.5. In these cases, too, all pairwise linkage disequilibria exist. The only similarity is in the mean fitness values. There are no similarities for the frequencies of gametes and the linkage disequilibria. For example: In one population, five FGs have been realized, but in two other populations six FGs occur. It is remarkable that all gamete frequencies are different. This fact shows clearly that the composition of the populations may be different even in a defined fitness system. In all populations the mean fitness has rather high, but different, values.

In fitness systems 7, 8 and 9, the existence of asymmetric equilibria with  $p_i = 0.5$  as well as  $p_i \neq 0.5$  has been shown, and at least 140 equilibrium situations are possible (60 with  $p_i = 0.5$  and 80 with  $p_i \neq 0.5$ ). The populations with equilibria of  $p_i = 0.5$  always have higher mean fitness values than populations with equilibria of  $p_i \neq 0.5$ . Thus the domains of attraction are presumably larger for these equilibria and consequently, in random initial situations, a population is more likely to get into such a domain. It is not surprising, therefore, that asymmetric equilibria with  $p_i \neq 0.5$  have been verified less often in the computer runs.

### 4. Comparison of the fitness systems

The fitness functions may be classified in the following way:

- According to the position of the steepest slope of the fitness function (Table 1, Figs. 1-10).
- According to the degree of heterozygosity at which the function has its maximum.

The results listed in Table 3 show similarities only if the first criterion is used. The fitness systems 1 and 2, 5 and 6 and also 7 to 9 can therefore be grouped together. Systems 3 and 4 can be regarded as transient systems of the neighbouring groups (Table 1).

A comparison with the results of the threshold model systems shows that system 11 has symmetric



equilibria in accordance with systems 1 and 2 (steepest slope occurs between 3 and 4 heterozygote loci). In contrast to systems 1 and 2, however, there are two more pairs of FGs (Table 1) in addition to the two most frequent gametes ( $g_i = 0.34$ ).

Similarly the system 12 (slope between 2 and 3 heterozygote loci) results in analogous situations to systems 5 and 6. The results of system 13 (slope between 1 and 2 heterozygote loci) are in complete agreement with those of the system 10.

The fitness systems 7, 8 and 9 (slope between 1 and 2 heterozygote loci) have equilibria between those of the systems 12 and 13. Presumably this can be traced back to the fact that the steep slope exceeds the heterozygote degree two (Table 1).

Generally it can be concluded that the number of FGs is greater the smaller the degree of heterozygosity at the point of the steepest slope of the function. Our fitness systems allow asymmetric equilibria with  $p_i = 0.5$ . In this case the quantity of gamete types with equal frequencies follows the series  $2^2, 2^3, 2^4$ . The extrapolation to more than five loci should allow additional categories of asymmetric equilibria with  $p_i = 0.5$  (up to  $2^{n-1}$ ). The fitness systems show in part additional asymmetric equilibria with  $p_i \neq 0.5$ . In situations where more than five loci are considered, new classes of equilibria would be expected.

Populations governed by the fitness systems investigated have, in the case of tight linkage, a remarkable increase in the mean fitness, which results in a decreased load. This effect is due to the deviation of the equilibria from the central solution under these conditions. An exceptional decrease in the load has to be expected in cases in which the genotypes formed by the frequent gametes have the degree of heterozygosity (i), which corresponds to the maximal value of the fitness system ( $w_i = 1$ ). As asymmetric equilibria exist in these cases, these genotypes are rare. Accordingly, the decrease in the load is small (9% and 12% resp., Table 3). In the other systems, among the most frequent genotypes are those with the highest

fitness value. Thus the load is decreased drastically (as much as 33%).

#### Acknowledgment

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